

## Factors affecting the structure and maturation of human tissue engineered skeletal muscle.

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### Public Summary:

Tissue engineered skeletal muscle has great utility in experimental studies of physiology, clinical testing and its potential for transplantation to replace damaged tissue. Despite recent work in rodent tissue or cell lines, there is a paucity of literature concerned with the culture of human muscle derived cells (MDCs) in engineered constructs. Here we aimed to tissue engineer for the first time in the literature human skeletal muscle in self-assembling fibrin hydrogels and determine the effect of MDC seeding density and myogenic proportion on the structure and maturation of the constructs. Constructs seeded with  $4 \times 10^5$  MDCs assembled to a greater extent than those at  $1 \times 10^5$  or  $2 \times 10^5$ , and immunostaining revealed a higher fusion index and a higher density of myotubes within the constructs, showing greater structural semblance to in vivo tissue. These constructs primarily expressed perinatal and slow type I myosin heavy chain mRNA after 21 days in culture. In subsequent experiments MACS<sup>(®)</sup> technology was used to separate myogenic and non-myogenic cells from their heterogeneous parent population and these cells were seeded at varying myogenic (desmin +) proportions in fibrin based constructs. Only in the constructs seeded with 75% desmin + cells was there evidence of striations when immunostained for slow myosin heavy chain compared with constructs seeded with 10 or 50% desmin + cells. Overall, this work reveals the importance of cell number and myogenic proportions in tissue engineering human skeletal muscle with structural resemblance to in vivo tissue.

### Scientific Abstract:

Tissue engineered skeletal muscle has great utility in experimental studies of physiology, clinical testing and its potential for transplantation to replace damaged tissue. Despite recent work in rodent tissue or cell lines, there is a paucity of literature concerned with the culture of human muscle derived cells (MDCs) in engineered constructs. Here we aimed to tissue engineer for the first time in the literature human skeletal muscle in self-assembling fibrin hydrogels and determine the effect of MDC seeding density and myogenic proportion on the structure and maturation of the constructs. Constructs seeded with  $4 \times 10^5$  MDCs assembled to a greater extent than those at  $1 \times 10^5$  or  $2 \times 10^5$ , and immunostaining revealed a higher fusion index and a higher density of myotubes within the constructs, showing greater structural semblance to in vivo tissue. These constructs primarily expressed perinatal and slow type I myosin heavy chain mRNA after 21 days in culture. In subsequent experiments MACS<sup>(®)</sup> technology was used to separate myogenic and non-myogenic cells from their heterogeneous parent population and these cells were seeded at varying myogenic (desmin +) proportions in fibrin based constructs. Only in the constructs seeded with 75% desmin + cells was there evidence of striations when immunostained for slow myosin heavy chain compared with constructs seeded with 10 or 50% desmin + cells. Overall, this work reveals the importance of cell number and myogenic proportions in tissue engineering human skeletal muscle with structural resemblance to in vivo tissue.

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